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Harnessing the Systemic Immunoinflammatory Index as a Potential Predictive Tool for Recurrent or Metastatic Nasopharyngeal Carcinoma Undergoing PD-L1 Inhibitor

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Purpose: Immunotherapy has become the primary option for recurrent and metastatic nasopharyngeal cancer (R/M NPC) after failure of chemotherapy, but without good prognostic indicators. Our study aimed to assess the potential of the systemic immune-inflammation index (SII) in predicting the effectiveness of PD-L1 inhibitor therapy for R/M NPC.

Patients and Methods: The study cohort comprises of a prospective Phase 2 clinical trial population undergoing PD-L1 inhibitor for R/M NPC at 42 hospitals in China between 2019 and 2021. The SII is classified into high and low states based on the optimal threshold determined by the ROC curve. We assessed the relationship between SII status and objective remission rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) using regression analyses and Kaplan–Meier method. We performed sensitivity analyses to confirm the results.

Results: Our study analyzed 153 patients from one of the largest cohorts to date of R/M NPC treated with PD-L1 inhibitor and found that SII showed a significant association with prognosis. We found higher ORR and DCR in the SII-Low group. Univariate analyses demonstrated that SII independently predicted DCR (OR, 0.43; 95% CI, 0.22–0.84; $p = 0.001$), PFS (HR, 1.85; 95% CI, 1.31–2.62; $p < 0.001$) and OS (HR, 1.92; 95% CI, 1.29–2.85; $p < 0.001$). After adjusting for covariates, multivariate analysis remains relevant. [DCR (OR, 0.47; 95% CI, 0.22–0.99; $p = 0.048$), PFS (HR, 1.72; 95% CI, 1.2–2.47; $p = 0.003$); OS (HR, 2.08; 95% CI, 1.38–3.13; $p < 0.001$)]. Sensitivity analyses also support this conclusion.

Conclusion: SII may well provide predictive value for the efficacy and prognosis of patients with R/M NPC treated with PD-L1 inhibitor. Patients with high status of SII may have a poorer therapeutic effect and survival.

Keywords: systemic immune response, nasopharyngeal carcinoma prognosis, immunotherapy, efficacy

Introduction

Nasopharyngeal carcinoma (NPC) is a tumor with high malignancy and mortality rates,[1] and is notably common in Southeast Asia, including southern China,[2,3] where about 4.4% to 14.8% of NPC patients present with distant metastases upon initial diagnosis.[4–6] Despite recent advancements in radiotherapy techniques and chemotherapeutic agents, the survival rate of NPC patients has not improved well.[7–9] However, the treatment of NPC recurrence and metastasis still

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faces great challenges.[10–12] Therefore, it has become imperative to seek more effective and promising treatment strategies.

Immunotherapy has brought about a revolution in cancer treatment in recent years., with significant breakthroughs achieved through the use of programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) immune checkpoint inhibitors (ICIs).[13] Such therapeutic agents are now standard of care in the treatment of R/M NPC, marking a key advance in the field.[14–16] KL-A167, a targeted PD-L1 immune checkpoint inhibitor, has been shown to be effective and safe in treating patients with R/M NPC who have failed first-line therapy.[17] Despite these achievements, challenges persist in accurately predicting treatment efficacy and devising personalized therapeutic approaches for this patient cohort.

Inflammation and immune regulation's interplay significantly influences disease progression and survival across various cancers.[18] Systemic inflammation correlates with alterations in peripheral blood leukocytes, which can be gauged using the Systemic Immunoinflammatory Index (SII),[19,20] calculates from neutrophil (N), lymphocyte (L), and platelet (P) counts using the formula: SII = N × P/L. The current study highlights that platelets play a crucial role in shielding circulating tumor cells (CTCs) from shear stress, aiding CTC transition, and facilitating extravasation of tumor cells to provide protection.[21,22] Neutrophils promote tumor progression by releasing growth factors like vascular endothelial growth factor, which promotes adhesion of tumor cells to distant organs.[23–26] Lymphocytes are essential in defending against tumors by enhancing cytotoxic cell death and restraining tumor cell proliferation and migration.[27–29] SII has been established as a prognostic factor in NPC treated with chemotherapy and radiotherapy.[30–32] In the present study, we further evaluated the prognostic value of SII in NPC patients receiving immunotherapy.

This study focuses on the first published and largest multicenter, prospective Phase II clinical trials of PD-L1 inhibitors in R/M NPC previously treated, to evaluate the predictive role of SII, a novel indicator that includes multiple mediators of inflammation.

Materials and Methods

Study Population

We conducted a post hoc analysis of data from a prospective phase 2 clinical trial conducted in 42 hospitals in the People's Republic of China. The clinical trial focused on the treatment of 153 patients diagnosed with histologically confirmed R/M NPC using KL-A167, a fully humanized monoclonal antibody PD-L1. This study adheres to the principles of the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines. The patient inclusion and exclusion criteria, along with the trial profile flowchart, are provided in the Supplementary File (Supplementary Figure 1).

Research Endpoints

The study assessed various endpoints, including Objective Remission Rate (ORR), Disease Control Rate (DCR), Progression-Free Survival (PFS), Overall Survival (OS). ORR was evaluated by the Independent Review Committee (IRC) according to RECIST V1.1 criteria, measuring the proportion of patients achieving partial remission (PR), and stable disease (SD). DCR measured the proportion of patients achieving complete response (CR), PR and SD. PFS represented the duration from the first PD-L1 inhibitor dose to disease progression or death. And OS defined the time from PD-L1 inhibitor drug initiation to death from any cause.

Data Analysis

Patients were categorized into high SII (SII > 1139) and low SII (SII ≤ 1139) status based on the optimal threshold value of SII determined from receiver operating characteristic (ROC) curves (Supplementary Figure 2). We first assessed the prognostic significance of inflammatory biomarkers on ORR and DCR by using logistic regression and calculated the corresponding hazard ratios (HR). We employed COX regression models to examine the relationship between various SII status and PFS as well as OS. Kaplan-Meier curves were utilized to compare the differences in OS and PFS between high

and low SII groups. Covariates with a p-value below 0.05 in univariate analyses were incorporated into the subsequent stepwise multivariate analysis.

We constructed multifactorial models incorporating significant and essential prognostic factors from the multivariate analyses to evaluate the predictive reliability of the SII for PD-L1 inhibitor therapy prognosis. The predictive performance of the SII and individual inflammatory mediators was evaluated using the area under the receiver operating characteristic curve (AUC-ROC) and compared with the predictive performance of component factors. We also used restricted cubic spline to flexibly model the relationship of SII with death and prognosis. Subsequently, we conducted tests to assess for potential effect modification by age, gender, smoking status, alcohol status, body mass index, ECOG PS and liver metastasis. Likelihood ratio tests were utilized to evaluate interaction on the multiplicative scale, while the relative excess risk caused by interaction was calculated to assess interaction on the additive scale.

All statistical analyses were performed using R 4.3.2 (R project, http://www.R-project.org/; accessed on 31 October 2023, version 4.3.2). Statistical significance was determined as a two-sided p-value below 0.05.

Results

Basic Clinical Information of Patients

Between February 26, 2019, and January 13, 2021, a cohort of 153 patients who had received at least one dose of PD-L1 inhibitor was analyzed across 42 medical institutions in China. The baseline characteristics of the patients are presented in Table 1. Among them, 94 individuals were categorized in SII-Low Group, and 59 in the SII-High Group. The median age of the patients was 49 years, ranging from 20 to 68. And the male proportion was relatively higher within the subpopulation (125 cases, 81.7%). At the initiation of the study, 82 out of 153 patients (53.6%) exhibited liver metastasis. ECOG scores were uniformly distributed between 0 and 1, with 94 cases (61.4%) scored as 1 (Table 1).

The median OS and PFS were 471 and 126 days for patients with SII ≤ 1139 and 303 and 43 days for patients with SII >1139 (Supplementary Table 1).

Table 1 The Comparisons of the Study Population with Different SII Status at Baseline

Variables	SII-low (n=94)	SII-high (n=59)	Overall	p value
	N(%)	N(%)	(N=153)	
Age (years)				0.123
Median(range)	49.0 [20.0, 68.0]	47.0 [26.0, 66.0]	49.0 [20.0, 68.0]	
Gender				0.465
Male	79 (84.0)	46 (78.0)	125 (81.7)	
Female	15 (16.0)	13 (22.0)	28 (18.3)	
BMI				0.606
≤18.5	16 (17.0)	13 (22.0)	29 (19.0)	
18.5~24	57 (60.6)	36 (61.0)	93 (60.8)	
≥24	21 (22.3)	10 (16.9)	31 (20.3)	
Tumor Stage				0.685
T0~2	30 (31.9)	22 (37.3)	52 (34.0)	
T3~4	33 (35.1)	17 (28.8)	50 (32.7)	
Tx	31 (33.0)	20 (33.9)	51 (33.3)	
Node Stage				0.988
N0~2	52 (55.3)	32 (54.2)	84 (54.9)	
N3	16 (17.0)	10 (16.9)	26 (17.0)	
Nx	26 (27.7)	17 (28.8)	43 (28.1)	

(*Continued*)

Table 1 (Continued).

Variables	SII-low (n=94)	SII-high (n=59)	Overall	p value
	N(%)	N(%)	(N=153)	
Smoking History				0.687
Current and former	36 (38.3)	19 (32.2)	55 (35.9)	
Never	58 (61.7)	40 (67.8)	98 (64.1)	
Alcohol History				0.982
Current and former	26 (27.7)	16 (27.1)	42 (27.5)	
Never	68 (72.3)	43 (72.9)	111 (72.5)	
Prior Radiotherapy				0.340
Yes	88 (93.6)	58 (98.3)	146 (95.4)	
No	6 (6.4)	1 (1.7)	7 (4.6)	
Prior radical chemoradiotherapy				
Yes	73 (77.7)	44 (74.6)	117 (76.5)	0.215
No	21 (22.3)	15 (25.4)	36 (23.5)	
ECOG PS				0.685
0	40 (42.6)	19 (32.2)	59 (38.6)	
1	54 (57.4)	40 (67.8)	94 (61.4)	
Liver Metastasis				0.480
YES	53 (56.4)	29 (49.2)	82 (53.6)	
NO	41 (43.6)	30 (50.8)	71 (46.4)	
LYMPH (10^9/L)				<0.001
Median(range)	0.94 [0.40, 1.97]	0.62 [0.12, 1.80]	0.83 [0.12, 1.97]	
PLT (10^9/L)				<0.001
Median(range)	189 [97.0, 357]	263 [109, 534]	218 [97.0, 534]	
NEUT (10^9/L)				<0.001
Median(range)	3.01 [1.10, 5.72]	4.84 [2.11, 13.8]	3.57 [1.10, 13.8]	

Notes: p-value was conducted with the chi-square test (categorical variables) and Mann–Whitney *U*-test (continuous variables), respectively.

Abbreviations: SII, systemic immune-inflammation index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BMI, Body Mass Index (calculated as weight in kilograms divided by height in meters squared); LYMPH, Lymphocyte Counts; PLT, Platelet; NEUT, Neutrophil.

Correlation Between SII Status and Treatment Efficacy

Patients classified as SII-LOW exhibited higher ORR and DCR at 21.6% and 51.6%, respectively, compared to 16.6% and 39% for those categorized as SII-High. (p=0.13 for ORR; p<0.001 for DCR, Figure 1A). We performed logistic regression analyses on the patients. The univariate analysis results revealed that patients with SII levels below 1139 (HR, 0.43; 95% CI, 0.22–0.84; P=0.001) exhibited superior disease control. In addition, ECOG score and liver metastases were risk factors for poor prognosis (Supplementary Table 2). After adjusting for other clinical characteristics, multivariate logistic regression analyses underscored the persistent significance of SII level as a potent independent prognostic factor (HR, 0.47; 95% CI, 0.22–0.99; P=0.048) (Figure 1B and C). SII was not statistically significant in predicting objective remission rates.

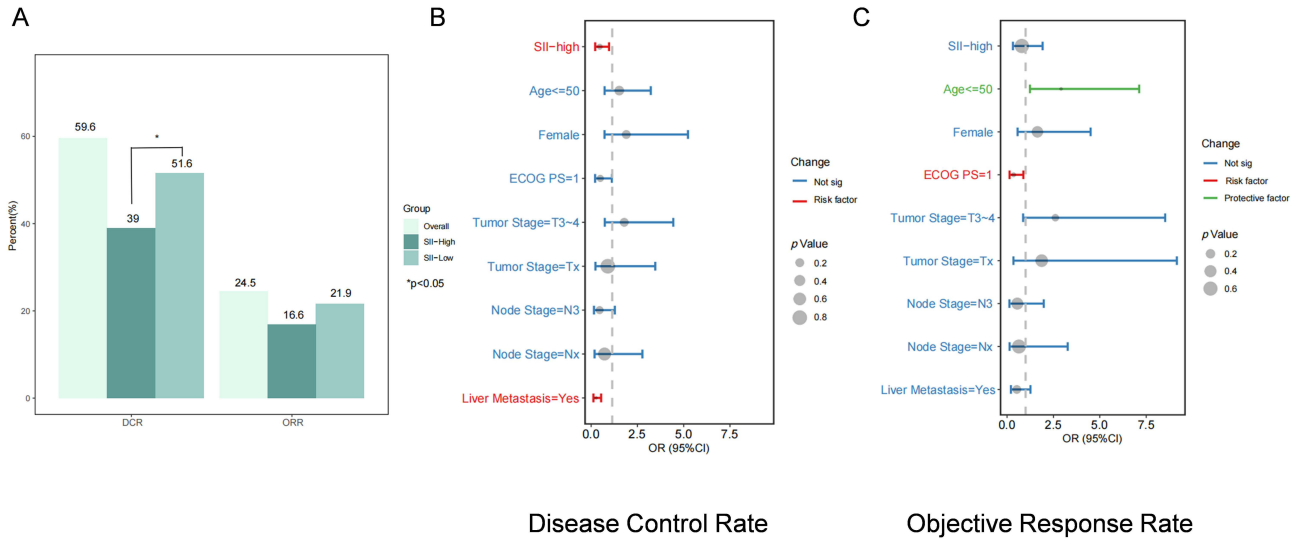

Figure 1 Treatment response and its multiple logistic regression analysis. (**A**) Results of DCR and ORR. (**B**) Multiple logistic regression for DCR. (**C**) Multiple logistic regression for ORR.

Correlation Between SII Status and Survival

High SII significantly correlated with reduced OS in R/M NPC in the study through univariate COX regression analyses (Supplementary Table 3). We also found that ECOG PS (HR=2.79, 95% CI, 1.79–4.33, P<0.001), BMI (HR=0.44, 95% CI, 0.27–0.7 P<0.001) and liver metastasis (HR, 2.57; 95% CI, 1.73–3.81; P<0.001) were independent risk factors affecting patient survival. In addition, sex, age, smoking history, alcohol consumption history, and stage had no significant effect on survival.

After adjusting for other clinical characteristics, multivariate COX regression analysis emphasized the sustained significance of SII status as a strong independent prognostic tool in the studied population (HR, 2.08; 95% CI, 1.38–3.13; P<0.001). Similar findings were observed regarding PFS, further supporting the robustness of SII level as a prognostic marker (Table 2).

Survival Analysis

High SII status correlated with lower PFS (HR, 1.85; 95% CI, 1.31–2.62; P<0.001) in the survival analysis, and similar results were found in OS (HR, 1.93; 95% CI, 1.30–2.85; P<0.001) (Figure 2A and B).

Table 2 A Multivariate Cox Proportional Hazards Model for Overall Survival and Progression Free Survival of Patients

Variables	Overall Survival		Progression-Free Survival	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	0.98 (0.96–1)	0.126	0.98 (0.97–1)	0.09
SII				
High	1.00 (Reference)		1.00 (Reference)	
Low	2.08 (1.38–3.13)	<0.001	1.72 (1.2–2.47)	0.003
Gender				
Male	1.00 (Reference)		1.00 (Reference)	
Female	0.7 (0.41–1.19)	0.185	0.79 (0.5–1.24)	0.297
Tumor Stage				
T0~2	1.00 (Reference)		1.00 (Reference)	
T3~4	1.06 (0.66–1.68)	0.817	0.81 (0.53–1.23)	0.323
Tx	1.85 (0.9–3.79)	0.092	0.97 (0.5–1.9)	0.933

(*Continued*)

Table 2 (Continued).

Variables	Overall Survival		Progression-Free Survival	
	HR (95% CI)	P value	HR (95% CI)	P value
Node Stage				
N0~2	1.00 (Reference)		1.00 (Reference)	
N3	1.18 (0.7–1.99)	0.531	1.3 (0.8–2.11)	0.284
Nx	0.59 (0.28–1.21)	0.149	1.26 (0.66–2.38)	0.485
ECOG PS				
0	1.00 (Reference)		1.00 (Reference)	
1	2.74 (1.66–4.52)	<0.001	1.58 (1.08–2.31)	0.018
Liver Metastasis				
Yes	1.00 (Reference)		1.00 (Reference)	
No	2.89 (1.89–4.42)	<0.001	1.77 (1.24–2.53)	0.002

Abbreviations: SII, systemic immune-inflammation index; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Predicting Effectiveness and Sensitive Analysis

The AUC values of the ROC curves indicated that the predictive value of SII's in terms of DCR, PFS, OS were better than that of single indicators of inflammation (Figure 2C–E). Among the components of SII, neutrophils had the highest AUC value and may be the most important factor influencing the survival prognosis of R/M NPC.

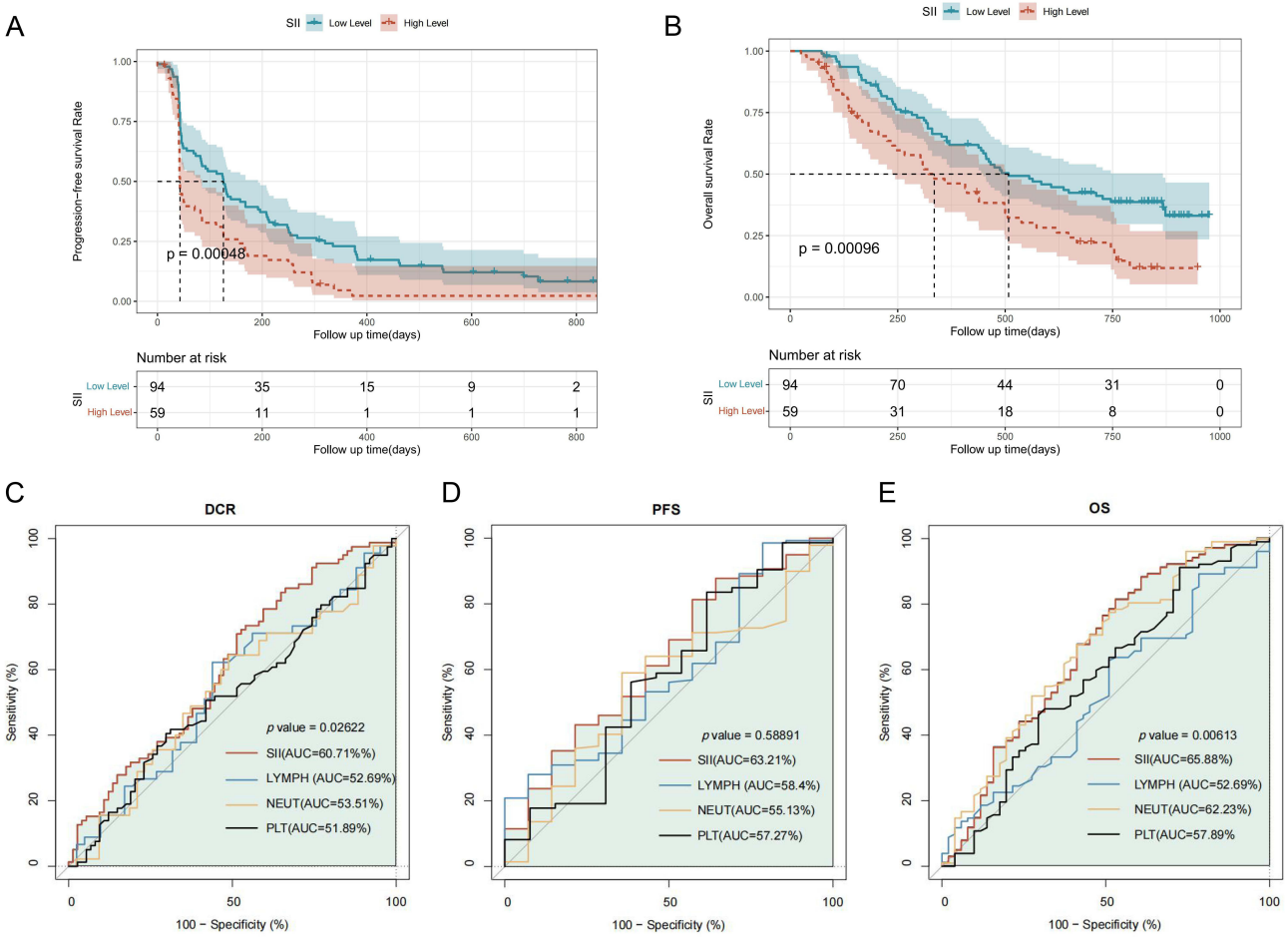

Figure 2 Assessment of survival based on different SII status and ROC curves. (**A**) The Kaplan-Meier curves show the OS of patients with different SII statuses. (**B**) The Kaplan-Meier curves show the PFS of patients with different SII status. (**C** – **E**) The discrimination of SII in predicting the survival and efficacy of patients. The receiver operating characteristic curve (ROC) shows the predictive value of SII with comparison to its components.

We used restricted spline plots to flexibly model and visualize the relationship between SII predicting ORR, DCR, PFS and OS. The Hazard Ratio of ORR fluctuated around 1 and was relatively insignificant, as shown in Figure 3A. With respect to the DCR with predicted treatment, Figure 3B shows that the DCR was good in the lower range of the SII, after which the rate of disease control declined (linear P = 0.158). The risk of PFS and OS was relatively flat until an SII of about 1330, after which it began to rise rapidly (nonlinear P = 0.016), similar to the findings for progression-free survival, as in Figures Figure 3C and D (Figure 3).

Subgroup and Interaction Analysis

Subgroup analyses indicated significant differences of the effect of some factors on the OS outcome (Figure 4). The OS was lower in men (HR: 2.41; 95% CI: 1.47–3.96) and individuals aged over 50 (HR: 0.47; 95% CI: 0.22–0.99). Additionally, lower survival rates were observed in individuals with a history of smoking and alcohol consumption, an ECOG score of 1, advanced Tumor Stage and Node Stage, BMI <24, and liver metastases. And there were no significant interactions between in these subgroups. Similar results were obtained from subgroup analysis of DCR and PFS. (Supplementary Figures 3 and 4)

Discussion

NPC is a common malignant tumor in the head and neck region, with a relatively high incidence.[1] Owing to its deep-seated location and the absence of early symptomatic manifestations, numerous cases are diagnosed in advanced stages, thereby presenting a formidable challenge for effective intervention.[6,33] Despite the historical efficacy of conventional radiotherapy and chemotherapy in managing nasopharyngeal carcinoma, their long-term and progression-free survival

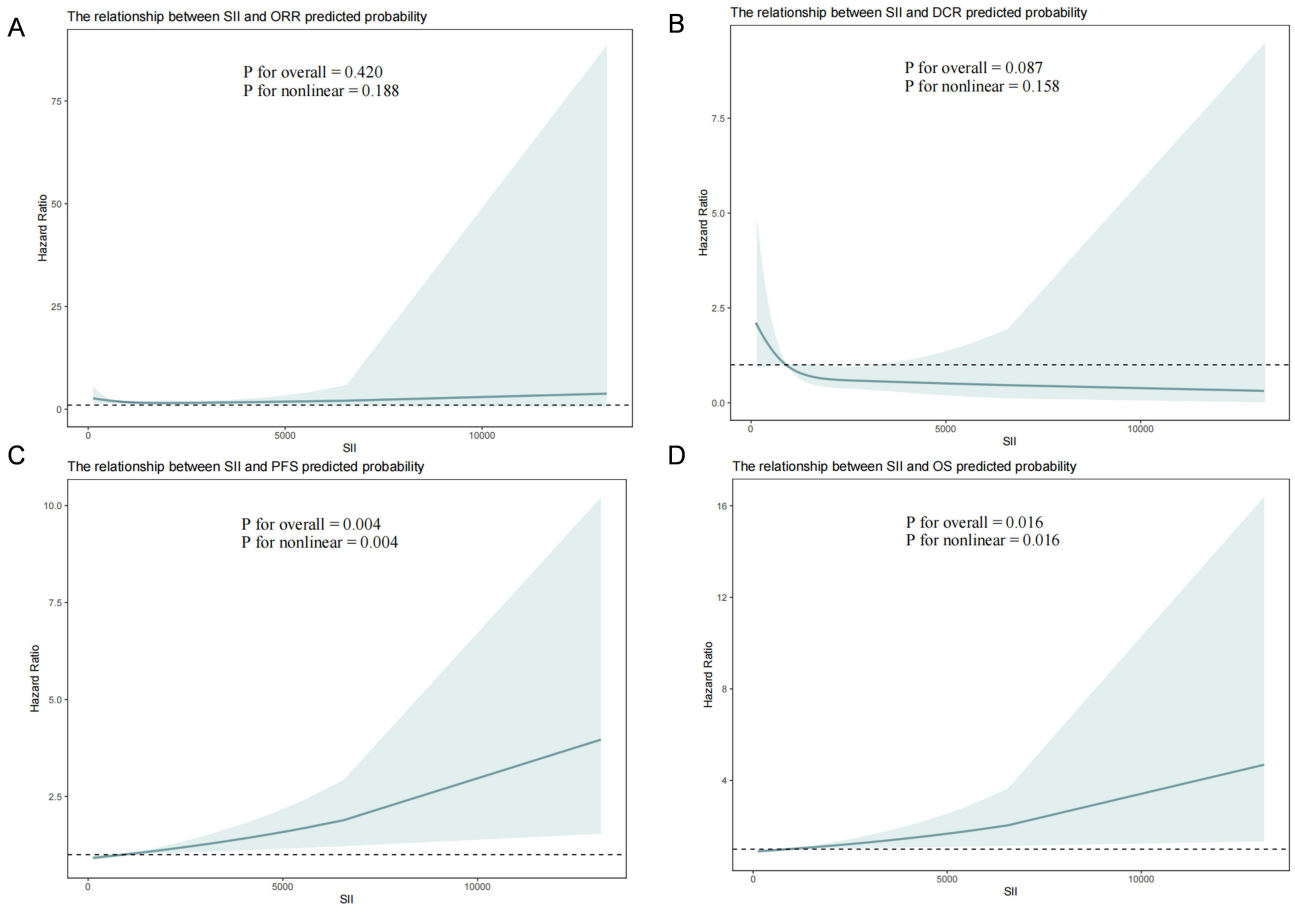

Figure 3 The restricted cubic spline (RCS) curves for SII and different endpoints. (**A**) SII Predicts RCS Curves for ORR. (**B**) SII Predicts RCS Curves for DCR. (**C**) SII Predicts RCS Curves for PFS. (**D**) SII Predicts RCS Curves for OS.

Subgroup	SII-Low	SII-High	Hazard Ratio	HR(95%CI)	*p* value	*p* value for interaction
All people	94	59		1.92(1.29−2.85)	<.001	
Age						0.199
≤50	55	40		1.33(0.67−2.62)	0.423	
>50	39	19		2.41(1.47−3.96)	<.001	
Gender						0.880
Male	79	46		1.90(1.23−2.94)	<.001	
Female	15	13		2.23(0.84−5.97)	0.115	
Alcohol History						0.113
Never	68	43		1.16(0.55−2.44)	0.713	
Current and former	26	16		2.36(1.48−3.78)	<.001	
Smoking History						0.318
Never	58	40		1.45(0.74−2.84)	0.281	
Current and former	36	19		2.24(1.37−3.67)	<.001	
ECOG PS						0.135
0	40	19		1.51(0.95−2.41)	0.082	
1	54	40		2.97(1.40−6.31)	<.001	
Node Stage						0.540
N3	16	10		1.83(1.18−2.85)	0.011	
Non−N3	78	49		2.49(1.01−6.11)	0.053	
Tumor Stage						0.459
T3~4	33	17		2.18(1.34−3.56)	<.001	
Tx & T0~2	61	42		1.55(0.79−3.07)	0.215	
BMI						0.178
≤18.5	16	13		2.98(1.32−6.75)	0.012	
18.5~24	57	36		2.00(1.17−3.41)	0.016	
≥24	21	10		1.05(0.43−2.54)	0.916	
Liver Metastasis						0.346
No	41	30		1.55(0.91−2.63)	0.120	
Yes	53	29		2.41(1.32−4.37)	<.001	

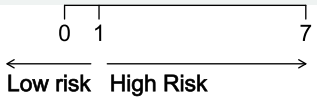

Figure 4 Subgroup analysis of Overall survival.

outcomes remain unsatisfactory.[8,10,11] In addressing this clinical impasse, immunotherapy has emerged as the established treatment approach for patients with recurrent or metastatic NPC as the second-line option. Notably, among the arsenal of immunotherapeutic agents, PD-L1 inhibitors have garnered considerable attention. The quest for robust biomarkers capable of delineating treatment response assumes paramount importance, thereby facilitating the stratification of patients and the tailoring of individualized treatment regimens.

This cohort represents the first and largest population examined to evaluate the prognosis and efficacy of PD-L1 inhibitors in R/M NPC who has been previously treated. In our multicenter retrospective cohort study, we have unveiled a significant association between baseline levels of inflammation-associated cells and survival and efficacy in the treated population. This underscores the intricate interplay between the tumor microenvironment and the response to immunotherapy. Emphasizing the pivotal roles of lymphocytes, platelets, and neutrophils in prognosticating survival and efficacy post-immunotherapy in R/M NPC, we highlight we highlight the promise of SII, combining these inflammatory markers, as a valuable prognostic tool. The SII may contribute to achieving equilibrium between tumor microenvironment inflammation and immune response. Moreover, the detection of biomarkers in blood holds promise in

circumventing the limitations of tumor tissue testing. Blood testing necessitates only a simple blood draw, boasts minimal invasiveness, permits multiple assessments, and facilitates dynamic monitoring of changes.

The conclusive demonstration of heightened inflammatory mediators' association with the heightened proliferation of cancerous cells, immune system modulation impacting adaptive responses, and diminished treatment efficacy collectively underscore their pivotal role in predicting mortality rates and prognosis among cancer patients.[18,21,34] Consequently, evaluating inflammatory mediators becomes a pivotal aspect of a comprehensive assessment aimed at predicting the outcome of immunotherapy for recurrent/metastatic NPC patients. Despite validating the predictive potential of SII in such patients, its practical application in daily clinical practice remains challenging.

In our current investigation, we observed a satisfactory predictive value of SII for both survival and efficacy in R/M NPC patients undergoing KL-A167. The ROC and RCS curves illustrated that SII exhibited superior predictive ability compared to inflammatory cells alone in identifying patients at high risk for NPC. The derived high SII linked to increased risk of from R/M NPC, as well as poor prognosis from immunotherapy, remained robust even after adjusting for a spectrum of potential confounders.

Furthermore, our analysis revealed that, among the components of SII, neutrophils and lymphocytes exhibited the highest discriminatory value in predicting survival in cancer patients. Previous studies have elucidated that neutrophils release immunosuppressive substances and promote the growth of blood vessels, supporting tumor cell invasion, and migration.[23–25,35] On the contrary, platelets shield tumors from immune cytotoxicity, promote epithelial-mesenchymal transition and enhance tumor cell movement and spread.[22,36] Meanwhile, lymphocytes play a pivotal role in immunotherapy by slowing tumor growth and promoting cell death.[29] Thus, the composite indicator SII, which combines three inflammatory mediators, correlates strongly with prognosis in patients receiving immunotherapy.

While there's a recognized link between SII and survival in NPC patients across different clinical settings,[31,32] only a few studies have investigated the correlation between SII during immunotherapy and mortality risk, as well as treatment effectiveness. Monitoring SII metrics in R/M NPC upon hospital admission may yield tangible clinical benefits, enhancing the survival rates of cancer patients. However, existing evidence primarily stems from studies of NPC patients receiving radiotherapy or a variety of different immunotherapies.[32,37–39] For example, a study based on SII and survival of nasopharyngeal cancer patients treated with PD-1 inhibitors showed a more significant association between SII status at cycle 3 after PD-1 inhibitor treatment and patient prognosis.[40] In addition, another study evaluating ICI-treated NPC patients found that baseline SII and the immunotherapy-related SII reduction was independent prognostic factor for PFS in advanced NPC patients receiving ICIs.[37]

Our study presents several noteworthy novelties. Firstly, it stands as the world's inaugural and largest investigation into assessing prognosis and the effectiveness of PD-L1 inhibitors in treating R/M NPC that has been previously treated. This pioneering endeavor validates the feasibility of employing the SII as a predictive tool for R/M NPC survival and furnishes a benchmark for clinical practice within Chinese medical centers. Secondly, we embark on exploring, for the first time in a Chinese population, the correlation between SII status and the efficacy of immunotherapy in R/M NPC. Moreover, advocating clinical intervention for cancer patients exhibiting elevated SII levels could significantly ameliorate SII status and prolong overall survival.

Admittedly, our study has some limitations. We note that despite being retrospective, the sample size from the prospective clinical trial as well as the follow up time remained constrained. While we observed differences in ORR post-PD-L1 inhibitor treatment for R/M NPC, subsequent regression analyses did not yield statistically significant results, likely due to sample size constraints or the period of observation. Furthermore, although we investigated the association between baseline SII levels and survival, we did not dynamically monitor SII trends during treatment, precluding assessment of its impact on patient prognosis. Additionally, our reliance solely on the composite inflammatory index overlooks potential synergies with other markers. The effect of EBV-mediated inflammatory response in NPC,[21,41] which is now also partially investigated by combining both types of metrics, EBV and inflammation,[42] in the prediction of survival. And uncontrolled covariates, such as detailed medical history, including prior surgeries and radiotherapy, may also influence cancer patient survival. Moreover, the majority of our study population presented with early to intermediate-stage cancers upon admission, necessitating further inquiry into whether advanced cancer patients could derive greater immunotherapy benefits. Future endeavors should prioritize prospective, large-scale, multicenter randomized

controlled trials to delve deeper into the immunotherapeutic mechanisms across varying SII inflammation indicators. Such efforts are critical for refining treatment strategies and enhancing patient survival outcomes.

Conclusion

SII holds promise as a predictive marker for both the efficacy and prognosis of patients with R/M NPC undergoing treatment with PD-L1 inhibitors. Elevated SII levels may signify a diminished therapeutic response and poorer survival outcomes. This finding underscores the clinical significance of incorporating SII assessment into treatment protocols for R/M NPC. By identifying patients with high SII levels early in the treatment process, clinicians can potentially tailor interventions to optimize therapeutic efficacy and improve patient survival. Therefore, integrating SII evaluation into routine clinical practice may enhance treatment decision-making and ultimately enhance outcomes for R/M NPC population receiving PD-L1 inhibitor therapy.

Abbreviations

AUC-ROC, Area under the receiver operating characteristic curve; BTC, Biliary tract cancer; BMI, Body Mass Index; CTCs, Circulating tumor cells; CR, Complete response; DCR, Disease control rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, Hazard ratios; IRC, Independent Review Committee; ICIs, Immune checkpoint inhibitors; L/LYMPH, Lymphocyte; N/ NEUT, Neutrophil; ORR, Objective remission rate; OS, Overall survival; PFS, Progression-free survival; PD-1, Programmed cell death protein 1; PD-L1, Programmed cell death ligand 1; PR, Partial remission; P/Platelet, PLT; R/M NPC, Recurrent and metastatic nasopharyngeal cancer; ROC, Receiver operating characteristic; RCS, Restricted cubic spline; SII, Systemic immune-inflammation index; SD, Stable disease.

Data Sharing Statement

The data that support the findings of this study are available from Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd (Chengdu, China), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd (Chengdu, China).

Ethics Approval and Informed Consent

Ethical approval for the collection of human data was obtained from the Institutional Review Board (HX-IRB-AF-12-V4.0) of West China Hospital. Prior to enrollment, all participants provided written informed consent. Registry and the Registration No. of the study/trial: KL-A167 clinical trial (NCT03848286). This study adheres to the principles of the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines.

Consent for Publication

Not applicable.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Junyou Ge, Yan Qing and Youneng Wei are employees of Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd (Chengdu, China). All other authors declare no potential conflicts of interest.

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